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SWIFTWATER, PA 18370

EXAMINER

NGUYEN, QUANG

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/829,004

Applicant(s)

PEDYCZAK ET AL.

Examiner

Quang Nguyen, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5-9, 12, 13 and 16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5-9, 12, 13 and 16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/04 has been entered.

Amended claims 5-9, 12-13 and 16 are pending in the present application, they are examined on the merits herein, with SEQ ID NO: 9 as the elected species.

Response to Applicants' amendment

In the amendment filed on 2/27/04, on page 5, line 4 Applicants state "Claim 20 was withdrawn by the Examiner in the Office Action dated 08/27/03". However, the withdrawn claim 20 **is not the same** as claim 20 presented in the amendment filed on 2/27/04 on page 4. Nevertheless, claim 20 was cancelled by Applicants in the Amendment filed on 2/27/04 (see page 2, lines 4).

Claim Objections

Claims 6-9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because

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the terms "comprising" and/or "having" in these claims have a broader scope than the term "consisting of" in claim 5 which claims 6 and 9 are dependent.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 5, 12-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new ground of rejection.**

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

Applicant's invention is drawn to an isolated nucleic acid molecule encoding an immunogenic peptide derived from prostate-specific antigen, the peptide being capable of **eliciting an immune response for treating prostate cancer and consisting of an**

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amino acid sequence as defined by Formula I: $X_n-X_1-X-X-X-X-X-X_2$ wherein $n=0$ or 1; each X_1 is independently selected from leucine or methionine; each X_2 is independently selected from valine or leucine; and each X is independently selected from any amino acid and analogs or derivatives of the PSA derived peptides; a composition for eliciting an immune response in an animal comprising an effective amount of the same nucleic acid molecule admixture with a suitable diluent or carrier and a method of eliciting an immune response in an animal comprising administering an effective amount of the same nucleic acid molecule.

Apart from the exemplification showing that PSA derived peptides that have SEQ ID NOS: 1-3 (with their respective encoding nucleic acid sequences of SEQ ID NOS: 7-9; and SEQ ID NO:9 as the elected species) are capable of stabilizing membrane-bound HLA-A0201 molecule and the peptide with SEQ ID NO:3 is also capable of eliciting an epitope-specific CTL response, the instant specification fails to teach a representative number of species for a broad genus of an isolated nucleic acid molecule encoding an immunogenic peptide derived from prostate-specific antigen consisting of an amino acid sequence defined by Formula I as claimed for eliciting an immune response for treating prostate cancer. It is also noted that the instant specification discloses two other PSA derived peptides having SEQ ID NOS: 4-5 that meet the criteria defined by Formula I, but they were found to be incapable of binding or stabilizing HLA-A0201 molecule (see example 1). Additionally, there are several factors that need to be considered for any potential tumor associated antigen epitope such as the ability of the candidate antigen to lodge into the peptide binding groove of a class 1

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MHC molecule, its sufficiently high binding affinity for the class I MHC molecule and a stable trimolecular complex of the peptide/class I MHC/B2-microglobulin complex displayed on antigen presenting cells; all of which are essential for the activation of appropriate CD8+ effector cells to yield an effective immunotherapeutic treatment; for this instance an immune response for treating prostate cancer. Moreover, at the effective filing date of the present application (4/10/2000), Altuvia et al. (Human Immunology 58:1-11, 1997) stated "Binding motifs, defined by anchor positions only, **have proven to be insufficient to ensure binding**, suggesting that other positions along the peptide sequence also affect peptide-MHC interaction"; and "The algorithm performs successfully in predicting peptide binding to MHC molecules with hydrophobic binding pockets but not when MHC molecules with hydrophilic, charged pockets are considered" (see abstract). Furthermore, Schirle et al. (J. Immunological Methods 257:1-16, 2001) also stated "**Reliable epitope prediction is still only available for a limited number of organisms and alleles** because little or no information is available about corresponding peptide specificities"; and "[w]hile the described strategies combining computational prediction and experimental methods are likely to provide a rapidly increasing number of T cell epitopes **as potential tools** for therapeutic and diagnostic purposes, the identified epitopes still have to pass the ultimate test; **they have to prove to be useful in the *in vivo* situation**" (see the section "Outlook" on page 11).

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the

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specification. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). Apart from a nucleic acid sequences of SEQ ID NOS: 7-9, with SEQ ID NO:9 as the elected species, a skilled artisan cannot fully envision the detailed structure of a broad genus of an isolated nucleic acid molecule encoding an immunogenic peptide derived from prostate-specific antigen consisting of an amino acid sequence defined by Formula I as claimed for eliciting an immune response for treating prostate cancer and a method of using the same for eliciting an immune response in an animal, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

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Amended claims 5, 12-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This is a new ground of rejection.**

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant claims are drawn to an isolated nucleic acid molecule encoding an immunogenic peptide derived from prostate-specific antigen (PSA), the peptide being capable of eliciting an immune response for treating prostate cancer and consisting of an amino acid sequence as defined by Formula I, its analogs or derivatives of the PSA derived peptide, with SEQ ID NO:9 as the elected species; a composition for eliciting an immune response in an animal comprising an effective amount of the same nucleic acid; and a method of eliciting an immune response in any animal comprising administering an effective amount of the same nucleic acid molecule to the animal.

The specification teaches by exemplification the nucleic acid sequences of SEQ ID NO:7-12 coding for PSA peptides of SEQ ID NO:1-6, respectively. Applicants further teach that of the six disclosed PSA peptides, 3 peptides having SEQ ID NO:1-3 bind

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HLA-A0201 molecules on T2 cells, whereas the other peptides do not bind to HLA-A0201 molecules on T2 cells. The CLP-312 peptide having SEQ ID NO:3 (encoded by SEQ ID NO:9) is selected as a representative PSA peptide to be injected subcutaneously into A2Kb transgenic mouse to assess the immunogenicity of the HLA-A0201 binding PSA peptide. The results showed that CLP-312 peptide is immunogenic and capable of eliciting an epitope-specific CTL response.

The above evidence has been noted and considered. However, the instant specification is not enabled for the presently claimed invention for the reasons discussed below.

(a) *The breadth of the claims.* The instant claims encompass any isolated nucleic acid molecule encoding an immunogenic peptide derived from prostate-specific antigen (PSA), the peptide being capable of eliciting an immune response for treating prostate cancer and consisting of an amino acid sequence as defined by Formula I, and analogs or derivatives of the PSA derived peptide with SEQ ID NO:9 as the elected species; a composition for eliciting an immune response in an animal comprising an effective amount of the same nucleic acid; and a method of eliciting an immune response in any animal comprising administering an effective amount of the same nucleic acid molecule to the animal.

(b) *The state of the prior art and the unpredictability of the art.* The nature of the instant claims falls within the realm of nucleic acid or genetic vaccine. At the effective filing date of the present application, the attainment of any therapeutic effect (e.g., eliciting an immune response for treating prostate cancer in this instance) via

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nucleic acid vaccine was and still is unpredictable. Leitner et al. (Vaccine 18:765-777, 2000; Cited previously) stated "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Moreover, with respect to the nature of the encoded immunogenic peptide derived from prostate-specific antigen of the present invention, it should be noted that there are several factors that need to be considered for any potential tumor associated antigen epitope such as the ability of the candidate antigen to lodge into the peptide binding groove of a class 1 MHC molecule, its sufficiently high binding affinity for the class 1 MHC molecule and a stable trimolecular complex of the peptide/class I MHC/B2-microglobulin complex displayed on antigen presenting cells; all of which are essential for the activation of appropriate CD8+ effector cells to yield an effective immunotherapeutic treatment; for this instance an effective immune response for treating prostate cancer in any animal. At the effective filing date of the present application, Altuvia et al. (Human Immunology 58:1-11, 1997) stated "Binding motifs, defined by anchor positions only, **have proven to be insufficient to ensure binding**, suggesting that other positions along the peptide sequence also affect peptide-MHC interaction"; and "The algorithm performs successfully in predicting peptide binding to MHC molecules with hydrophobic binding pockets but not when MHC molecules with hydrophilic, charged pockets are considered" (see abstract). Schirle et al. (J. Immunological Methods 257:1-16, 2001) also stated "**Reliable epitope prediction is still only available for a limited number of organisms and alleles** because little or

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no information is available about corresponding peptide specificities"; and "[w]hile the described strategies combining computational prediction and experimental methods are likely to provide a rapidly increasing number of T cell epitopes **as potential tools** for therapeutic and diagnostic purposes, the identified epitopes still have to pass the ultimate test; **they have to prove to be useful in the *in vivo* situation**" (see the section "Outlook" on page 11).

Additionally, at the effective filing date of the present application (4/10/2000) the prior art does not teach the use of SEQ ID NO:9, its analogs or derivatives or a composition comprising the same to elicit an immune response in any animal.

(c) *The amount of direction or guidance presented.* Apart from the exemplification showing that the CLP-312 peptide having SEQ ID NO:3 (an epitope having 9 amino acid residues encoded by SEQ ID NO:9) is immunogenic and capable of eliciting an epitope-specific CTL response in A2Kb transgenic mouse, the present disclosure fails to provide sufficient guidance for a skilled artisan on how the administration of the nucleic acid molecule of SEQ ID NO:9, its analogs or derivatives thereof in any animal would result in an induction of any effective immune response for treating prostate cancer, particularly as the claims being written, SEQ ID NO:9, its analogs or derivatives thereof, is not even operatively linked to any promoter or regulatory sequence for expression. As such, it is unclear how SEQ ID NO:9, its analogs or derivatives thereof could induce any effective immune response in any animal having any class I MHC molecule not necessarily limited to human HLA-A0201, to yield the therapeutic effects contemplated by Applicants, let alone for a broad genus

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of isolated nucleic acid molecule as claimed to be utilized in any animal. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so. Particularly, the attainment of any therapeutic effect via nucleic acid vaccine was and still is unpredictable in the art as already discussed above. Thus, in light of the state of the prior art at the effective filing date of the present application, coupled with the lack of sufficient guidance provided by the specification it would have required undue experimentation for a skilled artisan to **make and/or use** the isolated nucleic acid molecule, the composition and the method as claimed.

With respect to the breadth of a genus of the isolated nucleic acid molecule encoding an immunogenic peptide derived from prostate-specific antigen as claimed, apart from the exemplification showing that PSA derived peptides that have SEQ ID NOS: 1-3 (with their respective encoding nucleic acid sequences of SEQ ID NOS: 7-9; and SEQ ID NO:9 as the elected species) and that they are capable of stabilizing membrane-bound HLA-A0201 molecule and the peptide with SEQ ID NO:3 is also capable of eliciting an epitope-specific CTL response, the instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use the isolated nucleic acid molecule as broadly claimed. The unpredictability in making an encoded immunogenic peptide derived from prostate-specific antigen that is capable of eliciting an immune response for treating prostate cancer, wherein the encoded peptide consists of an amino acid sequence defined by Formula I of the present invention is clearly evident by the failure of two other PSA derived peptides having SEQ ID NOS: 4-5 to

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bind and stabilize HLA-A0201 (a human class I MHC molecule) even though both of them meet the criteria defined by Formula I (see example 1), let alone for binding to any class I MHC molecule in any animal. Moreover, in light of the teachings of Altuvia et al. and Schirle et al. as already discussed above, particularly their respective statements "Binding motifs, defined by anchor positions only, **have proven to be insufficient to ensure binding**, suggesting that other positions along the peptide sequence also affect peptide-MHC interaction" and "[w]hile the described strategies combining computational prediction and experimental methods are likely to provide a rapidly increasing number of T cell epitopes **as potential tools** for therapeutic and diagnostic purposes, the identified epitopes still have to pass the ultimate test; **they have to prove to be useful in the *in vivo* situation**" (see the section "Outlook" on page 11), it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention on the basis of this disclosure.

Furthermore, with respect to the breadth of the instant claims, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

(d) The quantity of experimentation provided. The instant specification fails to provide a single example including SEQ ID NO:9, its analog or derivative thereof, a

composition comprising the same to be capable of eliciting an immune response in any animal, let alone for the instant broadly claimed invention.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the unpredictability of the nucleic acid vaccine, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and/or use** the instantly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Schlom et al. (WO97/35021) for the same reasons already set forth in the previous Office Action.

With respect to the elected species of SEQ ID NO:9, Schlom et al. teach the preparation of a vector comprising at least one insertion site containing a DNA sequence encoding a prostate specific antigen oligo-epitope peptide, operably linked to a promoter capable of expression in a host cell, including prokaryotic and eukaryotic cells (pages 13-14). The DNA sequence encoding a prostate specific antigen oligo-epitope peptide contains or comprises or has SEQ ID NO:9 of the presently claimed invention (see SEQ ID NO:5 on page 64). Schlom et al. also disclose a method for

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inducing an immune response specific to PSA in the rhesus monkey model using a recombinant vaccinia virus containing the DNA sequence encoding a prostate specific antigen oligo-epitope peptide to kill prostatic cancer cells (page 17, lines 17-29). Although recombinant pox virus vectors are preferred, other recombinant viral vectors can be utilized including DNA viral vectors such as herpes virus and adenoviruses, and RNA viruses such as retroviruses and polio (page 15, lines 23-24). Schlom et al. also teach that the encoded antigen can be administered into the host with an adjuvant such as cytokines or co-stimulatory molecules or RIBI Deto, QS21 or incomplete Freund's adjuvant or with a suitable carrier such as liposome (page 17, lines 17-30), and that the recombinant vectors will typically be injected in a sterile aqueous or non-aqueous solution, suspension or emulsion in association with a pharmaceutically-acceptable carrier such as physiological saline (line 31 on page 19 continues to line 1 of page 20).

Due to the open language of the term "comprising" in claims 6 and 8-9; and the open language of the term "having" in claim 7; the teachings of Schlom et al. meet every limitation of these claims.

Accordingly, Schlom et al. anticipate the instant claims.

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Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on 2/27/04 (page 5) has been fully considered.

Applicants argue that Schlom's "oligo-peptide epitope peptide" includes sequence beyond that instantly claimed, and that claim 5 has been amended to delete reference to elongations.

Please note that the open language of the term "comprising" in claims 6 and 8-9; and the open language of the term "having" in claim 7; the breadth of these claims encompasses the teachings of Schlom et al. meet. Therefore, Schlom et al. still anticipate the instant claims.

Conclusion


No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.


DAVID GUZO
PRIMARY EXAMINER